REMARKS

Claims 8, 14, 15, 22, 33, and 37 have been amended. Claim 36 have been canceled. Claims 8, 14, 15, 22, 33, 34, 37 and 38 are pending. No new matter has been introduced herewith. The following addresses the substance of the Final Office Action.

Claim rejections under 35 U.S.C. §112

The Examiner has maintained rejections of Claims 8, 14, 15, 22 and has further rejected Claims 33, 34, and 36-38 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. More specifically, the Examiner believes that even though the human parkin2 shares a high percentage of sequence similarity with the mouse homologue, whether the mouse Parkin2 comprising the same mutation as the human would produce the same Parkinson's symptoms is unpredictable because the genetic control elements and genetic backgrounds of human and rodent are very different. The Examiner has invited the Applicant to provide recent references that teach that the phenotype of one transgenic specie is predictable of the same phenotype of another specie (i.e. from human to mouse). The Applicant had provided such references in the previous response to this Final Office Action, which was not entered by the Examiner. During the personal interview with the Examiner, conducted on June 28, 2004, the Examiner has maintained that the art of transgenic animals is unpredictable, and indicated that submission of data in the form of a Declaration under 37 C.F.R. §1.132 would be helpful in resolving the enablement issues raised by the Examiner. The Applicant is now submitting such a Declaration. In this document, the Inventor, Dr. Lubbert, provides data which shows an example of a transgenic mouse obtained by the claimed method. This transgenic mouse has a mutant parkin2 gene with a deletion of the exon 3, and it indeed exhibits behavioral impairments. This exemplary parkin2 mutant transgenic mice have reduced homecage activity, show deficit in habituation to a novel environmental contexts, have abnormality of dopaminergic system, and they also showed altered anxiety-related behavior in 2 separate tests (light-dark exploration and Morris water maze). Therefore, the transgenic parkin2 mouse as claimed is useful in investigating the role of parkin2 gene disruption on various types of animal behavior. Additionally, the Applicant has amended Claims 8 and 14 to recite specific mutations as described in the Specification as filed (Tables 1 and 2). Therefore, the Applicant asserts that the transgenic mouse as claimed in currently amended independent Claim 8 and the claimed method of the currently amended independent

Claim 14, as well as claims 15, 22, 33, 34, 37 and 38 which depend on Claims 8 or 14 are enabled and have utility.

The Examiner has also maintained that the Specification is not enabling for making a transgenic rat comprising mouse parkin2 mutation, because the references provided in the response to the previous Office Action filed April 25, 2003 do not teach generation of a transgenic rat involving rat embryonic stem cells. In the previous response to the Final Office action, which was not entered by the Examiner, the Applicants had provided new references to show that generation of a transgenic rat using embryonic stem cells was known at the time this invention was made. However, in order to speed the prosecution of this application the Applicants has now amended claims to not recite the "transgenic rat", therefore this rejection is now moot. The Applicant reserves the right to pursue the subject matter related to parkin2 transgenic rat in a related application.

The Examiner has rejected Claims 8, 14, 15, 22, 33, 34, 36-38 under 35 U.S.C. §112, first paragraph for allegedly lacking the written description. More specifically, the Examiner argues that the definition of a "homologue" of the mouse mutant parkin2 gene is lacking and that the Specification fails to describe a representative number of species by their complete structure or other identifying characteristics. The Applicant asserts that the Specification contains the definition of a homolog as "a homolog of said mutant mouse parkin2 protein wherein said homolog has an amino acid sequence having at least 70% amino acids identical to said mutant mouse parkin2 protein" (page 7, lines 19-29). However, to further the prosecution of this application, the Applicant has amended Claims 8, 14, 15, 22, 33, 34, 37 and 38 to now recite the specific mutations of mouse Parkin2 gene and protein as described in the Specification (Tables 1 and 2) and not to recite the homologues. The Applicant reserves the right to pursue the subject matter related to parkin2 homologues in a related application. Therefore, Claims 8, 14, 15, 22, 33, 34, 37 and 38 are now enabled, and withdrawal of the rejection of these claims is specifically requested.

The Examiner has rejected Claim 14 under 35 U.S.C. §112, second paragraph for omitting essential steps of how to produce a transgenic mouse or rat from the chimeric mouse or rat. More specifically, the Examiner has indicated that the method claim must include all essential steps and refer back to the preamble. Accordingly, Applicant has now amended Claim

14 to add such a step. Therefore, Claim 14 is now deemed complete and in condition for allowance.

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 112, and allowance of the pending application.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Final Office Action and as discussed during personal interview on June 28, 2004. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of the above amendments, remarks, and the Inventor's Declaration submitted herewith, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 23, 2004

By: _____

Marina L. Gordey
Registration No. 52,950
Agent of Record
Customer No. 20,995
(805) 547-5580

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STERN1.001APC PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Lubbert, H.
Appl. No.	:	09/830,703
Filed	:	April 26, 2001
For	:	TRANSGENIC ANIMAL MODEL FOR NEURODEGENERATIVE DISEASES
Examiner	:	Qian, Celine X.
Group Art Unit	:	1636

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. This Declaration is being submitted to demonstrate that a transgenic mouse having a copy of a mutated parkin gene indeed showed behavioral abnormalities that may be explored in relation to human Parkinson's disease.

2. I am the inventor on the above-identified patent application and am familiar with the specification and prosecution history.

3. I have extensive experience in the field of claimed invention as indicated in the attached Curriculum Vitae provided herewith as Exhibit A.

4. The claimed transgenic mouse has a parkin2 gene encoding mouse parkin2 protein, which is mutated in various regions of the gene as presented in the Tables 1 and 2 of the Specification. We have now tested an example of such a mouse. We first introduced a deletion of the exon 3 of the mouse parkin gene into embryonic stem cells, using standard techniques well-known in the art. We then injected the stem cells carrying the mutant parkin2 gene into blastocysts, and placed the blastocysts into a pseudopregnant mouse. We then obtained chimeric pups, which we bred to obtain heterozygotic animals. These heterozygotes were back-crossed to C57Bl/6J mice for four generations (F4). The F4 animals were then interbred to produce homozygous parkin knock-out animals and their wild-type littermates. We then confirmed that the parkin2 gene had indeed

been inactivated by performing Western blot analysis of brain homogenates from the transgenic animals with antibodies specific for parkin protein (Exhibit 1). Our data shows that while the parkin gene product is present in wild-type mice as well as in heterozygous mutants (in lower amount), parkin2 protein is absent in the brains of the parkin knock-out mice.

5. We analyzed the physical characteristics of the parkin knock-out mice, such as viability, body weight and brain morphology, and found no significant differences from the age- and gender-matched wild-type littermates (Exhibit 2).

6. We also found that parkin was not essential for the survival of nigral neurons in the knock-out mice (Exhibit 3).

7. We did, however, find behavioral impairments in parkin knock-out mice.

- We found that the parkin knock-out mice have a reduced homecage activity compared to their wild-type littermates (Exhibit 4).

- We tested naive mice on 3 separate days in the open field test. Wild-type (pa+/+) mice at 3 months exhibited locomotor habituation over time, showing reduced levels of activity on the second and third days relative to the first day (Exhibit 5A; $p<10^{-5}$). Parkin knock-out (pa-/-) mice at 3 months showed reduced behavioral response to novelty on the first day relative to their wild-type littermates (Exhibit 5A; $p<0.01$), and exhibited no habituation behavior in tests performed on the second and third days (Exhibit 5A). These results indicate that parkin knock-out mice have deficit in habituation to a novel environmental context.

- The time that mice spend in the center of the open field reflects anxiety-related behavior after repeated testing. Pa-/- mice spent less time in the center of the open field compared to pa+/+ mice in all three days of the tests (Exhibit 5B; $p<0.05$). A low dose of amphetamine (1 mg/kg) significantly reduced the time spent in the center by the wild-type mice (Exhibit 5B, $p<0,05$), but had no effect on pa-/- mice. This indicates abnormality of dopaminergic system in pa-/- mice.

- The difference in the anxiety-related behavior between parkin knock-out mice and their wild-type littermates was also observed in the light-dark exploration test, in which the mutant mice prefer to stay in the dark area, and had less transition than wild-type mice (Exhibit 6A; $p<0.001$; 6B; $p<0.01$).

- We also tested the mice in Morris water maze test. In learning to find the fixed hidden platform in Morris water maze, control and parkin knock-out mice exhibited comparable latency throughout 14 days spatial training (Exhibit 7A). On the probe trial, mice with both genotypes exhibited evidence for spatial learning, spending above chance time swimming in the platform quadrant (Exhibit 7B), and the two groups did not differ significantly. However, on a more stringent measure of spatial navigation, measured by counting the "crossing" wild-type (pa+/+) mice made significantly more crossings than parkin knock-out (pa-/-) mice. (Exhibit 7C; $p<10^{-5}$). Furthermore, pa-/- mice spent significantly more time in the outer annuli and significantly less time in the middle annuli than control mice (Exhibit 7D; $p<0.01$), indicating that knockout animals and controls used different platform-searching strategies and that parkin knock-out mice have an anxiety-related behavioral deficit in the water maze test.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: 29.7.04 By: _____

Hermann Lubbert

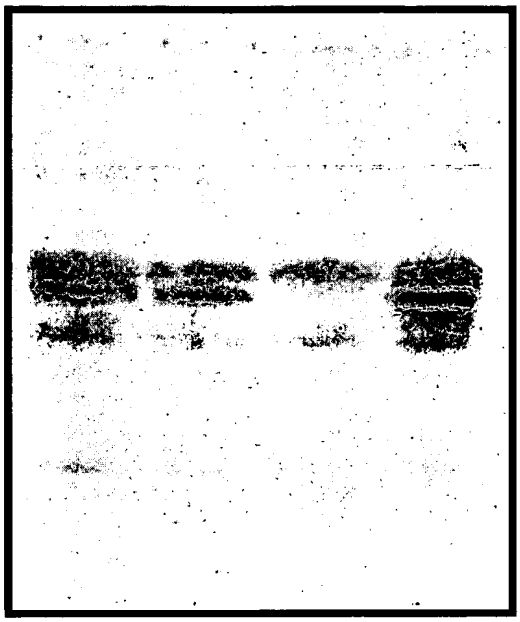

Exhibit 1. Western blot shows the absence of the parkin protein in the brains of parkin knock-out mice.

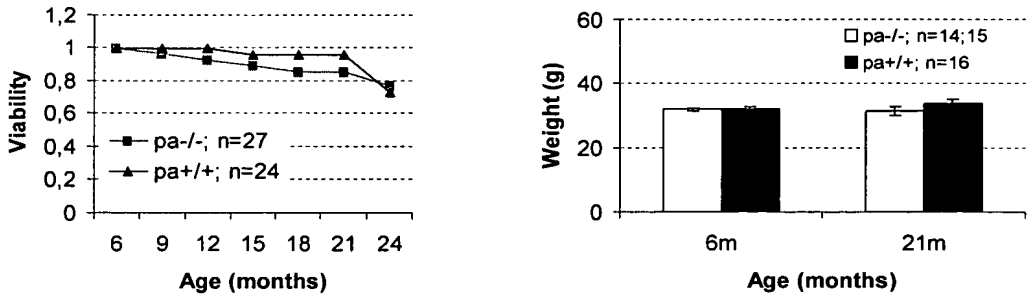

Exhibit 2. Parkin knock-out mice show normal viability and body weight

Exhibit 3. Summary of the cellular and biochemical characteristics of parkin knock-out mice. Levels of Dopamine in substantia nigra and striatum were similar between the parkin knock-out mice and the wild-type littermates

	at 3-24 month
Cell death in substantia nigra	no
Dopamine neurons in substantia nigra	normal
Dopamine innervation in striatum	normal
Dopamine-levels in substantia nigra and striatum	normal

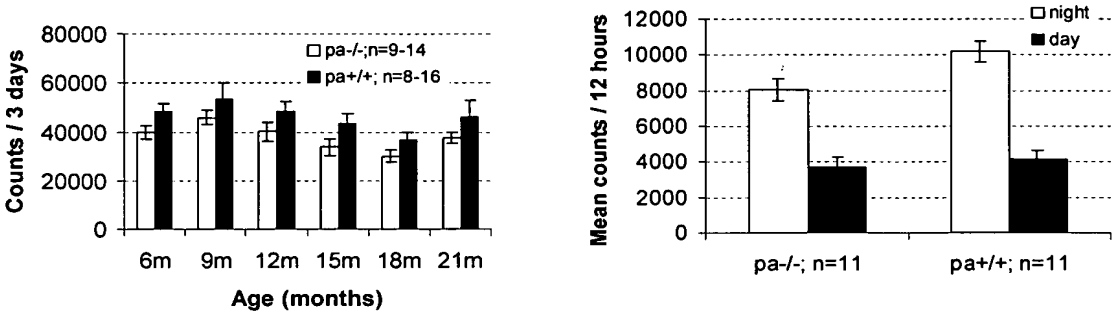

Exhibit 4. Parkin knock-out mice show reduced activity in homecage.

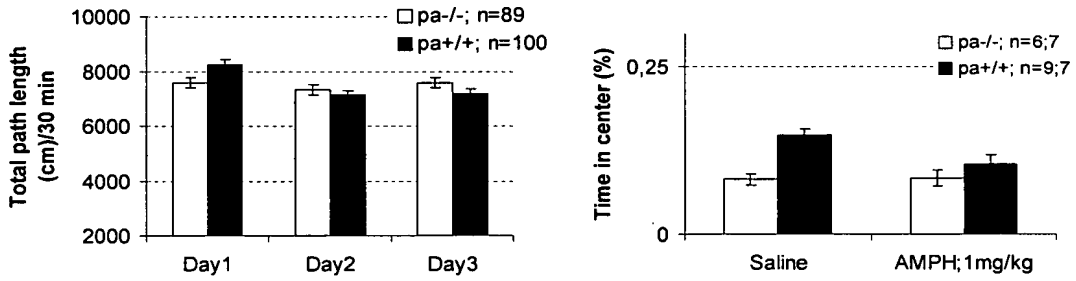

Exhibit 5. Parkin knock-out mice show abnormal habituation and anxiety behavior.

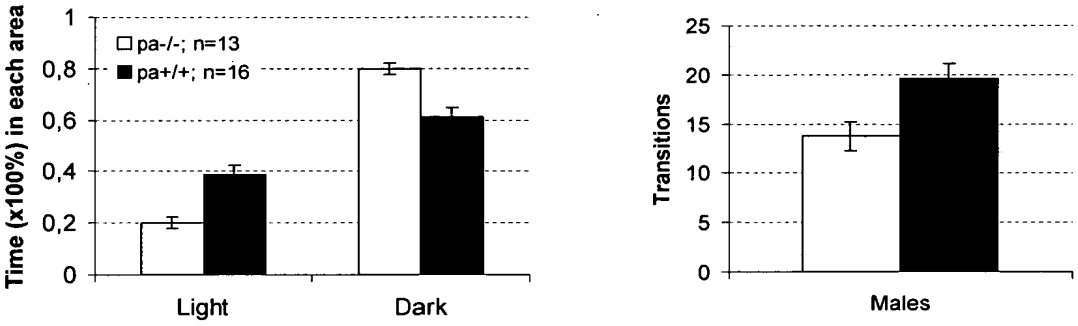

Exhibit 6. Anxiety-related abnormality of parkin knock-out mice in light-dark exploration test.

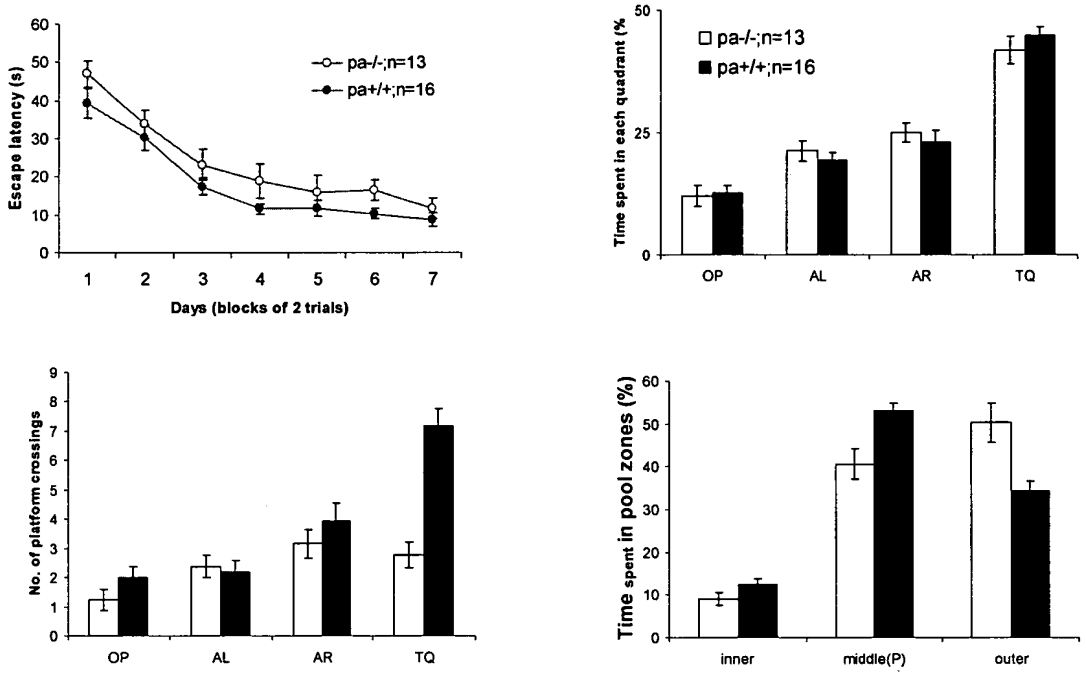

Exhibit 7. Anxiety-related deficit of parkin knock-out mice in water maze test.

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Exhibit A

CURRICULUM VITAE

HERMANN LÜBBERT

Born:	25. 3. 1956 in Cologne, Germany
Nationality:	German
Family:	Married, 4 Children
Education:	
1962-1966:	Grundschule Burscheid (Nordrhein-Westfalen)
1966-1974:	Städt. Gymnasium Wermelskirchen
May 1974:	Abitur
Military duty:	
October 1974 -December 1975	Military duty as flute player in "Heeresmusikkorps III", Lüneburg
University education:	
April 1976 -June 1980	Study of biology at University of Cologne Major subjects: 1. Genetics 2. Biochemistry 3. Organic Chemistry
June 1980 -August 1981	Diploma work in Prof. Walter Doerfler's group at the Institute for Genetics, University of Cologne Title: Klonieren und Kartierung des Genoms des Autographa californica Nuclear Polyhedrosis Virus. Untersuchungen an viraler RNA in infizierten Spodoptera frugiperda Zellen.
August 1981:	Diploma in biology with "sehr gut"
August 1981 -February 1984:	PhD work in Prof. Walter Doerfler's department at the Institute for Genetics, University of Cologne Title: Das Autographa californica Kernpolyedervirus als Modellsystem für die Untersuchung molekularbiologischer Mechanismen: Untersuchungen an Struktur und Organisation des viralen Genoms
February 1984:	PhD in natural sciences with "summa cum laude"
April 1994:	"Habilitation" and "Venia Legendi" at ETH in Zürich, Dept. Neurobiology
April 1998:	Awarded the title of "University professor"

Professional experience:

February 1984 -May 1984:	Research fellow in Prof. Walter Doerfler's group
June 1984 -May 1986:	"Research fellow" in Prof. Norman Davidson's group at California Institute of Technology, Dept. Chemistry, Pasadena, CA 91125, USA
June 1986 -September 1987:	"Senior research fellow" at California Institute of Technology, Dept. Biology, Pasadena, CA 91125, USA
October 1987 -February 1989:	Group head in the Dept. for Central Nervous System Research Sandoz Pharma AG, 4002 Basel, Switzerland
February 1989 -December 1994	Section head for research in neurodegenerative diseases, Sandoz Pharma AG, Basel
1990-1998:	Teaching duties in neurobiochemstry at Eidgenössischen Technische Hochschule (ETH), Zürich (in addition to the position at Sandoz)
January 1994 -December 1996:	Head of Department for Human Genome Research and Bioinformatics at Sandoz Pharma AG, Basel
January 1997 -December 1997:	Positions at Novartis: Head of Dept. for Neurogenetics (Personnel responsibility for about 40 people), Member of the "Neuroscience Management Team" (heading all neurosciences at Novartis), Scientific Expert Molecular Neurobiology (representing this discipline at global research managment of Novartis)
Since April 1998:	Chairman of the Dept. of Animal Physiology, Ruhr-University Bochum, 44780 Bochum, Germany (parallel to position at Biofrontera)
Since February 1998:	CEO of Biofrontera AG, Hemmelrather Weg 201, 51377 Leverkusen, Germany

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